Mark C. Udey, MD, PhD *Feature Editor*

Thrombocytopenia, multiple mucosal squamous cell carcinomas, and dyspigmentation

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CASE SUMMARY

History

A 30-year-old woman was seen in consultation in the Dermatology Clinic at the National Institutes of Health Clinical Center, in Bethesda, Maryland, for skin hyperpigmentation and hypopigmentation. At birth, she was noted to be small for gestational age, with microcephaly and bilateral absence of thumbs and radii. At 5 years of age, the patient underwent corrective hand and wrist surgery and was found to be profoundly thrombocytopenic. The thrombocytopenia persisted and she subsequently developed progressive anemia, which did not respond to prednisone and anabolic steroids. At age 9, she received an allogeneic bone marrow transplant from her HLA-matched brother and achieved engraftment of donor stem cells with correction of her marrow failure. An investigation into the patient's short stature at the age of 12 years revealed both growth hormone deficiency and hypothyroidism. Shortly thereafter, the patient developed increased intracranial pressure due to an intracranial lipoma, necessitating placement of a ventriculoperitoneal shunt. Later in adolescence she was diagnosed with hypogonadism, hyperlipidemia, type 1 diabetes mellitus, and cataracts. During a recent evaluation, she underwent a liver biopsy for persistent abnormal liver enzymes and was diagnosed with cirrhosis secondary to nonalcoholic steatohepatitis.

At the time of presentation, the patient had a history of multifocal oral leukoplakia with involvement of the gingiva, buccal mucosa, tongue, and palate. She also reported multiple squamous cell carcinomas of the tongue* as well as in situ squamous cell carcinoma of the scalp. In addition, she had a history of vulvar papillomatosis consistent with human papillomavirus infection and a history of squamous cell carcinoma of the vulva.

The patient's medications at the time of evaluation included insulin, simvastatin, levothyroxine, metoclopramide, esomeprazole, ursodiol, and montelukast. Her family history was notable for Ashkenazi Jewish heritage.

Physical examination

The patient's general examination was significant for markedly short stature (4 feet, 5 inches), microcephaly, microphthalmia, and micrognathia. Her thumbs were absent, and her forearms were approximately one third of their expected length (Fig 1). She had clinodactyly and an abnormal crease pattern of the palms. The index fingers had been surgically altered to function as thumbs.

Scalp hair was fine and had a brown gray hue. There were several light brown macules ranging in size from 1 to 2 cm on the patient's trunk and lower extremities (Fig 2, *A*). The axillae and neck were hyperpigmented with dozens of tightly clustered hypopigmented macules (Fig 2, *B*). Several hyperkeratotic papules and plaques, some of which had a verrucous surface, were present on the hands and feet.

Oral examination revealed white and red plaques on the lateral buccal mucosa (Fig 3), as well as

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*Squamous cell carcinoma of the tongue in this patient was reported previously by Jansisyanont, Pazoki, and Ord (Squamous cell carcinoma of the tongue after bone marrow transplantation in a patient with Fanconi's anemia. J Oral Maxillofac Surg 2000;58:1454-7).

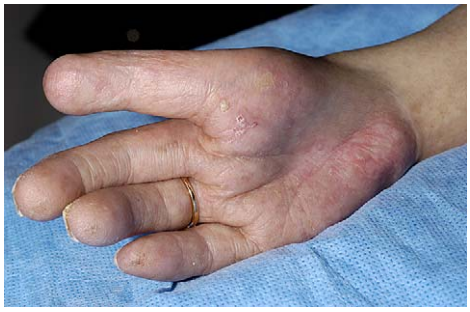

Fig 1. Congenital absence of thumb. The second finger has been surgically altered to function as a thumb. Keratotic papules are present on the palm.

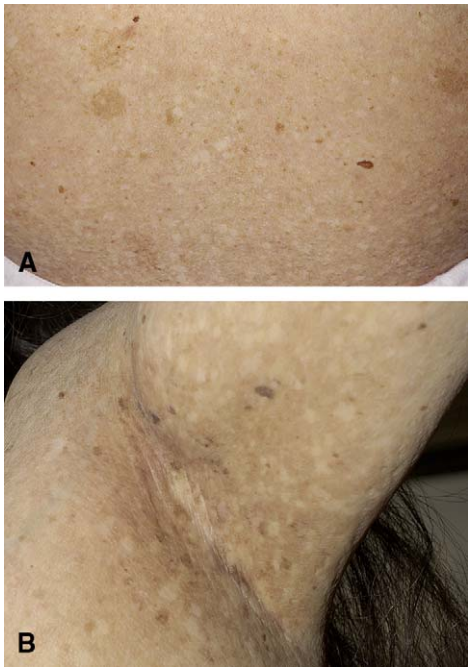

Fig 2. Dyspigmentation of Fanconi anemia. **A**, Several irregular café-au-lait macules, smaller fine tan hyperpigmented macules, and dozens of guttate hypopigmented macules on the lower back. **B**, Hyperpigmentation of left axilla with discrete hyperpigmented and hypopigmented macules.

scattered white plaques on the gingiva and dorsal surface of the tongue. A nodular firm lesion was present on the left lingual tonsillar area, near a site of previous squamous cell carcinoma excision.

Significant diagnostic studies

Radiographic examination of the upper extremities revealed bilateral absence of the thumbs and radii (Fig 4). In addition, the ulnae were bowed and very short compared with the humeri. Computed tomography of the abdomen and pelvis identified bilateral pelvic kidneys.

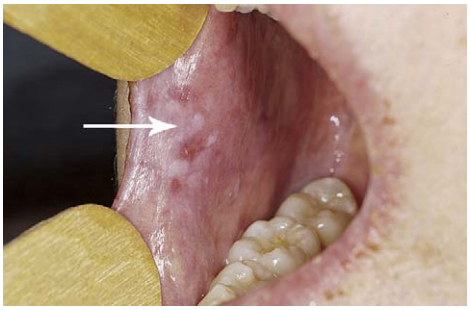

Fig 3. Oral leukoplakia on right buccal mucosa (*arrow*).

Diagnosis

Fanconi anemia (FA).

Follow-up

The nodular lesion of the left lingual tonsillar area was found to be a recurrent squamous cell carcinoma for which she is currently receiving treatment. The patient continues to undergo regular surveillance for the development of new malignancies.

DISCUSSION

FA (Mendelian Inheritance in Man [MIM] No. 227650) is an uncommon autosomal-recessive disorder, although more than 1300 cases of varying severity have now been reported in the medical literature.[1] A founder mutation in *FANCC* (IVS4+4 A>T) (MIM No. 227645) is associated with a carrier frequency of 1 in 89 in Ashkenazi Jews, but FA has been reported in all racial and ethnic groups.[2,3] Important clinical features include bone marrow failure, skeletal malformations, and a predisposition to the development of malignancies, particularly acute myeloid leukemia, squamous cell carcinomas of the oral mucosa and female genitalia, and liver neoplasms.[1,2] However, FA is both genetically and phenotypically diverse. Patients may demonstrate only subclinical hematopoietic disease or, similar to our patient, present with classic features of the disorder, including congenital skeletal defects, early-onset bone marrow failure, endocrine abnormalities, premalignant leukoplakia, and oral and genital squamous cell carcinoma.

Dyspigmentation is a common cutaneous feature of FA and usually is present at birth or develops in early childhood. Approximately 55% to 75% of patients with FA have altered cutaneous pigmentation, which manifests as café-au-lait macules, hyperpigmented macules, or "guttate" hypopigmented macules.[2,4] Hyperpigmentation tends to be accentuated in intertriginous areas and typically darkens with age. Darkening of the skin may also result from iron overload after repeated red blood

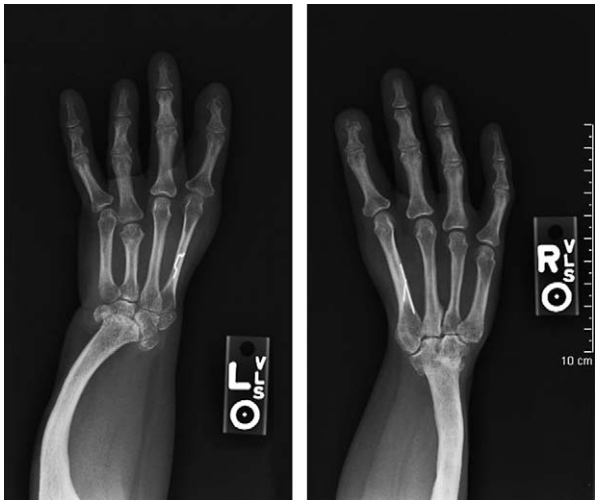

Fig 4. Absence of thumbs, several carpal bones, and radii, and marked bowing of ulnae bilaterally.

cell transfusions.[5] Other less common cutaneous findings include Sweet's syndrome[6] and cutaneous amyloidosis.[7]

Skeletal malformations, including hypoplasia of the thumbs, radial hypoplasia, hip dysplasia, and scoliosis, occur in more than two thirds of FA patients.[2,8] Other frequent congenital features include short stature, microphthalmia, and renal deformities, such as ectopic or horseshoe kidney.[2,8] A broad nose, epicanthal folds, and micrognathia characterize the typical facies of an FA patient. Approximately 80% of patients exhibit endocrine abnormalities, most commonly growth hormone insufficiency, hypothyroidism, and diabetes mellitus.[9]

The most common presentation of FA is progressive bone marrow failure, which develops in approximately 90% of patients and usually appears early in childhood at a mean age of 8 to 9 years. The median life expectancy of an FA patient is approximately 30 years, and the most frequent cause of death is bone marrow failure.[10] Aplastic anemia may be managed effectively in many patients with androgens or growth factors, whereas others eventually require stem cell transplantation. Acute myeloid leukemia is the most common malignancy observed in FA patients, occurring primarily in teens and young adults. Patients who survive into early adulthood are at high risk for solid organ cancer with a cumulative incidence of 75% of one or more solid tumors by age 48.[11] Squamous cell carcinoma of the head and neck is the most frequently reported malignancy, followed by carcinoma of the vulva and uterine cervix. Liver tumors are also relatively common.

Patients with FA have features of two types of cancer predisposition syndromes: the autosomal recessive disorders of DNA repair, which include ataxia telangiectasia, xeroderma pigmentosum, Bloom syndrome, Werner syndrome, Rothmund Thomson syndrome, and Nijmegen breakage syndrome, as well as the inherited bone marrow failure syndromes, which include dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, severe congenital neutropenia, and amegakaryocytic thrombocytopenia. FA cells are exquisitely sensitive to chromosome breakage and cytotoxicity induced by DNA cross-linking agents. To date, 12 complementation groups (FA-A, FA-B, FA-C, FA-D1, FA-D2, FA-E, FA-F, FA-G, FA-I, FA-J, FA-L and FA-M) and 11 FA genes (*FANCA, FANCB, FANCC, FANCD1 [BRCA2], FANCD2, FANCE, FANCF, FANCG, FANCJ/BRIP1, FANCL* and *FANCM*) have been associated with FA. The gene defective in complementation group FA-I has not yet been identified. Approximately 70% of FA patients have mutations in *FANCA*, 10% in *FANCC*, and 10% in *FANCG*; mutations in the other genes are rare. The exact role of the FA genes in DNA repair and the link to the pathogenesis of the congenital abnormalities, bone marrow failure, and oncogenesis in FA patients is an area of active ongoing investigation.

Up to one third of patients with FA may not demonstrate obvious congenital abnormalities and are not diagnosed until another sibling is affected or a hematologic problem or cancer develops; however, most patients manifest subtle dermatologic signs of FA.[8] Therefore early recognition of the cutaneous features of FA is of significant value. Annual bone marrow examination after diagnosis may allow for an early diagnosis of myelodysplasia or leukemia. Liver function tests and ultrasound examination are recommended to identify patients with adenomas or hepatomas before they become symptomatic, and direct visualization of the oropharynx and fiberoptic endoscopy for aerodigestive malignancy and precancerous lesions should be performed regularly. Finally, gynecologic examination is recommended beginning at menarche for all female patients.

KEY TEACHING POINTS

- FA is an autosomal recessive disease characterized by bone marrow failure, congenital skeletal malformations, and a predisposition to hematologic and solid organ malignancies. Oral findings include premalignant leukoplakia and squamous cell carcinoma. Cutaneous findings include multiple café-au-lait macules and diffuse hyperpigmented and hypopigmented macules.
- There are 12 known complementation groups, each with great phenotypic heterogeneity.

- Early diagnosis of FA is helpful in order to initiate appropriate malignancy surveillance, treatment for bone marrow failure, and genetic counseling for family members.

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Editor's note: Dr Alter is a leading authority on inherited bone marrow failure syndromes, including FA, dyskeratosis congenita, Shwachman-Diamond syndrome, and Diamond-Blackfan anemia. For more information on the NCI Inherited Bone Marrow Failure Syndrome protocol, visit www.marrowfailure.cancer.gov. Clinicians can refer interested patients to the NIH patient recruitment and referral office at 800-411-1222 or by e-mail at prpl@mail.cc.nih.gov.

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